Mild parenchymal lung disease is still lung disease

Reply to L. Godinas and co-workers:

We would like to offer our thanks to L. Godinas and co-workers for their interest in our study "Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension" [1].

The receipt of a referral of a patient with echocardiographic evidence of significant precapillary pulmonary hypertension (PH), unremarkable spirometry, no thromboembolic disease and an absence of a relevant associated medical condition, but with a mild degree of parenchymal lung disease, is a not uncommon occurrence in a high-volume referral centre. Often, the referrer will comment that the mild lung disease is insufficient to "cause" the PH. Patients with severe parenchymal lung disease and/or severely abnormal spirometry can be assigned a diagnosis of PH due to chronic lung disease (CLD-PH) with confidence [2]. However, the correct diagnosis and role of pulmonary arterial hypertension (PAH)-specific therapy in patients with much milder amounts of parenchymal lung abnormalities and preserved spirometry may be less clear. The 6th World Symposium on Pulmonary Hypertension concluded that patients with severe PH but only modest parenchymal lung disease and preserved spirometry should be considered to have PAH [3]. Furthermore, pivotal randomised controlled trials (RCTs) for PAH therapies have excluded patients with moderate to severe abnormalities in spirometry but have not made any reference to the presence of parenchymal lung disease or to diffusing capacity of the lung for carbon monoxide (D_{LCO}) [4, 5].

We therefore set out to investigate what effect the presence of only mild parenchymal lung disease has in patients who would be defined as having IPAH according to the 6th WSPH recommendations. As L. Godinas and co-workers summarise, we observed a group of patients ($IPAH_{mild\text{-}LD}$) characterised by preserved spirometry and a lack of airflow obstruction (meaning that many did not meet diagnostic criteria for COPD), minor/mild parenchymal lung disease, a low D_{LCO}, a lack of improvement in exercise capacity and quality of life following PAH therapy, and a poor prognosis. They propose that these patients represent the previously described "pulmonary vascular phenotype" [6]. It has previously been recognised that a small proportion of patients with COPD have severe PH but only moderate airflow obstruction (forced expiratory volume in 1 s of around 50% predicted) and have a circulatory limitation to exercise [7–9]. Kovacs *et al.* [6] therefore proposed a "pulmonary vascular phenotype" characterised by severe precapillary PH, moderate airflow limitation and low D_{LCO} (<45% predicted). The majority of patients in the $IPAH_{mild\text{-}LD}$ cohort described in our study do not fulfil these spirometric criteria. Nevertheless, we agree that they have many similarities to the "pulmonary vascular phenotype", especially with respect to their low D_{LCO} and severe PH. We also observed a group of patients with no apparent parenchymal or spirometric lung disease who had an isolated reduced D_{LCO} (<45% predicted) in the absence of other known causes of reduced diffusion, such as systemic sclerosis or pulmonary veno-occlusive disease ($IPAH_{DLCO<45}$). Future histological studies should help clarify whether the proposed "vanishing capillary syndrome" is indeed the cause for the marked reduction in D_{LCO} in both these groups of patients [10].

In conclusion, we agree with L. Godinas and co-workers that the patient groups described in our study are distinct from patients with "true" IPAH. These data should help inform decisions regarding the use of PAH therapies and referral for transplantation. We also agree that RCTs of pulmonary vascular therapies in these patients are sorely needed. Furthermore, we would argue that D_{LCO} and computed tomography findings should be incorporated in inclusion and exclusion criteria for future RCTs for PAH therapies.

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Response to correspondence regarding the recent paper: "Mild parenchymal lung disease and/or low diffusion capacity impacts survival and treatment response in patients diagnosed with idiopathic pulmonary arterial hypertension" https://bit.ly/2Gy6Dco

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Robin Condliffe [1,2], David G. Kiely [1,2] and Robert A. Lewis[1,2]
[1]Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, UK. [2]Dept of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, UK.

Correspondence: Robin Condliffe, Sheffield Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, UK. E-mail: robin.condliffe@nhs.net

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